Regulation of Specific Chromosomal Boundary Elements by CTCF Protein Complexes in Human Embryonic Stem Cells

Grant Award Details

Regulation of Specific Chromosomal Boundary Elements by CTCF Protein Complexes in Human Embryonic Stem Cells

Grant Type: SEED Grant

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Investigator:

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Institution:	Salk Institute for Biological Studies
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $647,343

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Progress Reports

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View Report

Grant Application Details

Application Title: Regulation of Specific Chromosomal Boundary Elements by CTCF Protein Complexes in Human Embryonic Stem Cells

Public Abstract:

The genetic information contained in all human cells is arranged into distinct territories or "neighborhoods" with barriers or "fences" that protect the action in one neighborhood from spilling over into an adjacent region. In this way, one gene (A) can be working while its neighboring genes (B and C) are resting. As physiological conditions change in the body, appropriate signals are transmitted to cells that instruct genes to alter their genetic "programming" by opening or closing the fences. This allows gene A to be turned off and genes B and C to start working. Importantly, these "fences" can control large numbers of genes that regulate critical cellular processes. For example, a well-known fence borders a chromosomal region containing genes that encode oxygen-carrying hemoglobin. By opening or closing this fence, hemoglobin synthesis, and our oxygen carrying ability, can be turned on or off. Many, as yet, unidentified fences are likely to exist in our genetic material. This proposal is designed to find the fence(s) that border certain genes (Nanog-Stellar-GDF3) that are important to maintain stem cells in their most plastic state that is, having the ability to become any other cell type. Once we identify the borders/fences of this chromosomal region, we plan to investigate how they are themselves switched on or off. This switch is very likely to depend upon specific proteins that interact with the fences or borders and serve as "latches" to keep the gates open or closed and the Nanog gene working or resting. Information about the exact proteins or "latches" that control the Nanog neighborhood will enable us to begin to devise strategies, through genetics or pharmacological means, to open or close this particular fence at will and regulate the activity of the Nanog gene. The ability to maintain an active Nanog gene may facilitate stem cell self-renewal or reprogram adult somatic cells to progenitors that are more easily directed to another cell type. By contrast, the capacity to turn off the Nanog gene may be important for the treatment of stem cells that have acquired tumorigenic potential through persistent Nanog expression and inappropriate self-renewal. In the larger scope, information from this proposal may serve as a platform by which unique proteins that control other fences can be identified. Pharmacological manipulation of these unique proteins may selectively control the activity of chromosomal neighborhoods that specify distinct cell fates.

Statement of Benefit to California:

All of our genetic information that regulates the proper function of our tissues and our overall health is arranged in large territories or "neighborhoods" that can be turned on or off with a genetic switch called a boundary. This acts like a fence to separate the influence of one neighborhood which may be working (active) from an adjacent one which may be resting (inactive). Organ function or tissue "identity" is conferred by the exact combination of our 35,000 genes that are working or resting. Diseased organs or tissues, including cancers, are characterized by having the wrong combination of genes that are inappropriately active or inactive. By being able to control the activity of chromosomal regions ("territories") through switches or boundaries , we hope to devise new ways to more easily turn on and off many genes that determine tissue identity and proper organ function. This may lead to new therapeutic strategies to repair existing diseased tissues or replace them with new cells.
